APPENDIX

Clin Cancer Res. 2003 Jan;9(1):10-9.

The statins as anticancer agents.

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3-Hydroxy-3-methylgutaryl CoA reductase inhibitors, commonly referred to as the statins, have proven therapeutic and preventative effects in cardiovascular diseases. Recently, there are emerging interests in their use as anticancer agents based on preclinical evidence of their antiproliferative, proapoptotic, anti-invasive, and radiosensitizing properties. Inhibition of 3-hydroxy-3-methylgutaryl CoA reductase by the statins interferes with the rate-limiting step of the mevalonate pathway, leading to reduced levels of mevalonate and its downstream products, many of which play important roles in critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression. Perturbations of these processes in neoplastic cells by the statins may therefore result in control of tumor initiation, growth, and metastasis. The statins have demonstrated growth inhibitory activity in cancer cell lines and preclinical tumor models in animals. Phase I trials of statins in humans have demonstrated myotoxicity as their main dose-limiting toxicity, and Phase II trials in various tumor types are ongoing to evaluate their efficacy. Potential future directions in the development of the statins as anticancer agents include combinations with chemotherapeutic or other molecular-targeted agents, combinations with radiotherapy, maintenance therapy in minimal disease status, and as chemopreventive therapy.

Publication Types:
Review
Review, Tutorial

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Potential anticancer effects of statins: fact or fiction?

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Deregulation of any of the steps in cell growth, proliferation and apoptosis may result in its malignant transformation. Statins, along with their lipid-lowering potential, modify several processes in the cell cycle. These agents inhibit cell proliferation and arrest cell cycle progression by interrupting growth-promoting signals. Statins selectively induce proapoptotic protential in tumor cells and synergistically enhance proapoptotic potential of several cytotoxic agents. Statins alter angiogenic potential of cells by modulating apoptosis inhibitory effects of VEGF and decrease secretion of metalloproteases. Statins also alter adhesion and migration of tumor cells, thereby inhibiting tumor invasion and metastasis. Statins suppress rate of activation of multiple coagulation factors and thus prevent coagulation-mediated angiogenesis. Statins have been shown to have anti-tumor activity in experimental models. Various anti-neoplastic properties of statins are probably a result of inhibition of posttranslational modifications of growth regulatory proteins. Molecular mechanisms of antiproliferative, proapoptotic and antiangiogenic effects of statins are reviewed in this chapter.

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Potential antitumor effects of statins (Review).

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Statins, which have been introduced to the clinic for the treatment of hypercholesterolemia, are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the major rate-limiting enzyme that controls the conversion of HMG-CoA to mevalonic acid (MA). MA is the precursor in the biosynthesis of isoprenoid compounds including cholesterol, dolichol and ubiquinone. Furthermore, mevalonate-derived prenyl groups enable precise cellular localization and function of many proteins such as Ras and Rho proteins. Therefore, besides lowering cholesterol level, statins exert pleiotropic effects on many essential cellular functions including cell

proliferation, differentiation, and survival but also participate in the regulation of cell shape and motility. Statins have been shown to inhibit proliferation and to induce apoptosis in a variety of tumor cells. They have also been found to display antitumor effects against melanoma, mammary carcinoma, pancreatic adenocarcinoma, fibrosarcoma, glioma, neuroblastoma, and lymphoma in animal tumor models resulting in retardation of tumor growth, and/or inhibition of the metastatic process. In preclinical studies statins have also been demonstrated to potentiate the antitumor effects of some cytokines and chemotherapeutics. The molecular mechanisms underlying antitumor activity of statins have not been fully elucidated but interference with the function of Ras and Rho family GTPases, inhibition of the activity of certain cyclin-dependent kinases (CDK), and activation of CDK inhibitors, all seem to participate in this activity. The results of several clinical studies of statins in cancer patients including phase I, phase I/II, and phase II trials have been published. Although evaluation of the therapeutic efficacy is not the purpose of early clinical trials and all conclusions might be premature at this stage, some preliminary conclusions have already been drawn. The results of these studies do not show any significant therapeutic effects of statins in cancer patients. However, the results of one of these studies suggest that statins could effectively strengthen the therapeutic activity of some chemotherapeutics. This observation seems to agree with the results of preclinical studies. However, as toxic side effects of statins have been particularly evident in their combination with some other drugs great caution should be advised while planning clinical trials based on combination therapy including statins in cancer patients.

Publication Types:
Review
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Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention.

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Pools of farnesyl diphosphate and other phosphorylated products of the mevalonate pathway are essential to the post-translational processing and physiological function of small G proteins, nuclear lamins, and growth factor

receptors. Inhibitors of enzyme activities providing those pools, namely, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase and mevalonic acid-pyrophosphate decarboxylase, and of activities requiring substrates from the pools, the prenyl protein transferases, have potential for development as novel chemotherapeutic agents. Their potentials as suggested by the clinical responses recorded in Phase I and II investigations of inhibitors of HMG CoA reductase (the statins), of mevalonic acid-pyrophosphate decarboxylase (sodium phenylacetate and sodium phenylbutyrate), and of farnesyl protein transferase (R115777, SCH66336, BMS-214662, Tipifarnib, L-778,123, and, prematurely, perillyl alcohol) are dimmed by dose-limiting toxicities. These nondiscriminant growth-suppressive agents induce G1 arrest and initiate apoptosis and differentiation, effects attributed to modulation of cell signaling pathways either by modulating gene expression, suppressing the post-translational processing of signaling proteins and growth factor receptors, or altering diacylglycerol signaling. Diverse isoprenoids and the HMG CoA reductase inhibitor, lovastatin, modulate cell growth, induce cell cycle arrest, initiate apoptosis, and suppress cellular signaling activities. Perillyl alcohol, the isoprenoid of greatest clinical interest, initially was considered to inhibit farnesyl protein transferase; follow-up studies revealed that perillyl alcohol suppresses the synthesis of small G proteins and HMG CoA reductase. In sterologenic tissues, sterol feedback control, mediated by sterol regulatory element binding proteins (SREBPs) 1a and 2, exerts the primary regulation on HMG CoA reductase activity at the transcriptional level. Secondary regulation, a nonsterol isoprenoid-mediated fine-tuning of reductase activity, occurs at the levels of reductase translation and degradation. HMG CoA reductase activity in tumors is elevated and resistant to sterol feedback regulation, possibly as a consequence of aberrant SREBP activities. Nonetheless, tumor reductase remains sensitive to isoprenoid-mediated post-transcriptional downregulation. Farnesol, an acyclic sesquiterpene, and farnesyl homologs, gamma-tocotrienol and various farnesyl derivatives, inhibit reductase synthesis and accelerate reductase degradation. Cyclic monoterpenes, d-limonene, menthol and perillyl alcohol and beta-ionone, a carotenoid fragment, lower reductase mass; perillyl alcohol and d-limonene lower reductase mass by modulating translational efficiency. The elevated reductase expression and greater demand for nonsterol products to maintain growth amplify the susceptibility of tumor reductase to isoprenoids, therein rendering tumor cells more responsive than normal cells to isoprenoid-mediated growth suppression. Blends of lovastatin, a potent nondiscriminant inhibitor of HMG CoA reductase, and gamma-tocotrienol, a potent isoprenoid shown to post-transcription-ally attenuate reductase activity with specificity for tumors, synergistically affect the growth of human DU145 and LNCaP prostate carcinoma cells and pending extensive preclinical evaluation, potentially offer a novel chemotherapeutic strategy free of the dose-limiting toxicity associated with high-dose lovastatin and other nondiscriminant mevalonate pathway inhibitors.

Publication Types:
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